

Consensus statement on use of reversal agents for factor Xa inhibitor–related bleeding

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Executive summary

Vizient® convened an expert panel of clinicians to critically appraise the literature and provide consensus-based, expert opinion on the utilization of pharmacological reversal agents for factor Xa inhibitor–related major bleeding. A modified Delphi technique was used to drive consensus.

Using the Institute for Clinical and Economic Review Evidence Rating Matrix, the panel reached consensus on comparative effectiveness ratings for andexanet alfa vs standard of care (evidence is promising, but inconclusive) and for andexanet alfa vs prohemostatic agents (evidence is insufficient or inconclusive). Consensus was not reached for the effectiveness of prohemostatic agents (prothrombin complex concentrate, activated prothrombin complex concentrate) vs standard of care.

Consensus was reached on the following topics: indications for pharmacological reversal, clinical scenarios in which one pharmacological reversal agent may be favored, use of combination therapy, operational advantages and disadvantages of pharmacological reversal agents, off-label use, and cost as a consideration for utilization.

1. Introduction

1.1 Purpose of panel

Andexanet alfa (coagulation factor Xa [recombinant] inactivated-zhzo; Andexxa, Alexion Pharmaceuticals) is a specific factor Xa inhibitor reversal agent and the only medication approved by the US Food and Drug Administration (FDA) for reversal of apixaban and rivaroxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.¹ Although they are not FDA approved, nonspecific hemostatic agents — prothrombin complex concentrate (PCC; various manufacturers) and anti-inhibitor coagulant complex or activated prothrombin complex concentrate (aPCC; FEIBA, Takeda) — are frequently used off label for reversal of factor Xa inhibitors. After andexanet alfa was approved, multiple European and American guideline committees updated their guidance to preferentially recommend its use for reversal of life-threatening or uncontrolled bleeding due to rivaroxaban or apixaban, based on the FDA approval and the specific mechanism of reversal.²⁻⁶ However, not all guideline committees have made a preferential use recommendation, citing the low degree of certainty in the evidence of the effects of any of the pharmacological agents used for reversal of factor Xa inhibitor–associated major bleeding.⁷

Because of the lack of agreement among professional organizations regarding use of andexanet alfa in therapy as well as its high cost compared with nonspecific prohemostatic agents, many Vizient members have expressed a need for guidance on using andexanet alfa in a rational, evidence-based manner. The practice of evidence-based medicine integrates the best external clinical evidence with individual, clinical expertise. To this end, Vizient convened an expert panel of clinicians to critically appraise the literature and provide consensus-based, expert opinions on the utilization of pharmacological reversal agents for factor Xa inhibitor–related major bleeding.

1.2 Materials and methods

Selection of participants

Between April and May 2020, a group of clinicians was selected to participate based on their publication history, direct clinical experience in the management of factor Xa inhibitor reversal, or both. If an invited clinician was unable to participate but recommended a colleague who met the selection criteria, the colleague was invited to participate.

To recruit emergency department, critical care, and other clinicians with anticoagulation expertise who practice in Vizient member hospitals, Vizient solicited additional participants through its monthly pharmacy newsletter, which has a circulation of more than 30,000. All clinicians who responded and submitted a curriculum vitae underwent a structured interview. A panel of 3 Vizient pharmacists made the final selection of expert participants.

Methods of consensus

A modified Delphi technique was used to drive consensus.⁸ A first round of questions, developed by Vizient pharmacists with anticoagulation expertise, was sent to the panelists on June 4, 2020. This first round was separated into 2 domains: literature review and expert opinion. In the first, participants were asked to provide an evidence rating for each of the reversal agents compared with standard of care and with each other using the Institute for Clinical and Economic Review (ICER) [Evidence Rating Matrix](#).⁹ The matrix takes into account both the magnitude and direction of net health benefit and the level of certainty (conceptual confidence interval) of the best point estimate of the net health benefit. All outcomes were assessed qualitatively. In the second domain, panelists were asked to share their expert opinion on a series of questions related to the clinical application of reversal agents, operational considerations, and cost or value of reversal agents.

Responses to the first round of questions were presented in a blinded fashion to panel participants during a 2-hour virtual meeting on June 17, during which Vizient pharmacists facilitated discussion. As a result of this meeting, a revised questionnaire was sent on July 7 that asked panelists to evaluate the net health benefit of reversal agents based on the ICER Evidence Rating Matrix and vote on a series of revised expert opinion statements informed by the panel discussion. Agreement by 60% of the panel members was considered a consensus.

2. Comparative clinical effectiveness

2.1 Overview

To inform the expert panel's analysis of the comparative clinical effectiveness of pharmacological interventions for reversal of factor Xa inhibitor–related major bleeding, evidence was abstracted from observational and interventional trials that met the following criteria: (1) enrolled adult patients (age ≥ 18 years) who were taking a direct factor Xa inhibitor (apixaban, betrixaban, edoxaban, rivaroxaban); and (2) evaluated the safety and effectiveness of PCC (3- or 4-factor), aPCC, or andexanet alfa for management of a major hemorrhage occurring at any location. Although a comparison with standard of care (i.e., supportive measures in addition to discontinuation of the direct factor Xa inhibitor) was considered desirable, a comparator arm was not required as there is a dearth of such studies. The panel's review focused on surrogate and clinical outcome measures of effectiveness such as hemostatic efficacy and functional outcome (i.e., modified Rankin scale, all-cause mortality) as well as potential harms (thromboembolism and other adverse events).

2.2 Methods

Data sources and searches

A structured search of PubMed (1966-May 2020), ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials was conducted to identify relevant studies for inclusion. All searches were limited to reports in the English language; articles indexed as guidelines, reviews, editorials, or case reports were excluded. All search strategies were generated based on a PICO framework: population, intervention, comparator, and

outcomes. The search strategy included a combination of indexing terms (MeSH and supplementary terms) and free-text terms.

To supplement the database search, reference lists of included trials were manually checked. Additionally, all panel participants provided references germane to the review. Non-peer-reviewed literature (e.g., conference proceedings) was not included.

Selection of eligible studies

Study selection was based on abstract and full text review. Three pharmacists reviewed abstracts for the selected citations; if the abstract provided insufficient evidence to determine whether the trial should be included, the full text was retrieved. No abstract was excluded because of inadequate evidence. Trials that evaluated anticoagulants other than factor Xa inhibitors were excluded if reversal results were not reported separately for each pharmacologic class of anticoagulants.

Data extraction strategy

Data from trials were extracted into evidence tables by 2 pharmacists. Criteria from the US Preventive Services Task Force were used to categorize the quality of the clinical trials as:

- **Good** — Studies that met all criteria: Comparable groups were assembled initially and maintained throughout the study (follow-up \geq 80%); reliable and valid measurement instruments were used and applied equally to all groups; interventions were spelled out clearly; all important outcomes were considered; and appropriate attention was given to confounders in analysis. In addition, intention-to-treat analysis was used for randomized controlled trials (RCTs).
- **Fair** — Studies that had any or all of the following problems but did not have the fatal flaws noted in the “poor” category below: Generally comparable groups were assembled initially but questions remained about whether some (although not major) differences occurred during follow-up; measurement instruments were acceptable (although not the best) and generally applied equally; some but not all important outcomes were considered; and some but not all potential confounders were accounted for. Intention-to-treat analysis was used for RCTs.
- **Poor** — Studies with any of the following fatal flaws: Groups assembled initially were not close to being comparable or were not maintained throughout the study; unreliable or invalid measurement instruments were used or instruments were not applied equally among groups (including not masking outcome assessment); and key confounders were given little or no attention. Intention-to-treat analysis was lacking for RCTs. Case series and noncontrolled cohort studies were considered “poor.”

2.3 Results

Evidence tables are available by request at pharmacyquestions@vizientinc.com. Data extracted from studies included study design, inclusion/exclusion criteria, number of patients, baseline characteristics, bleeding location, reversal agent and dose, laboratory data, hemostatic efficacy (including definitions and methods of assessment), functional outcome, all-cause mortality, thromboembolic events, and adverse events. There are no randomized, prospective, controlled comparisons for any of the reversal agents; therefore, all studies were rated as poor quality because of the lack of a control arm.

Across all studies, populations were heterogeneous (all-comer rather than based on inclusion and exclusion criteria) and definitions of hemostatic efficacy, the primary outcome for many of these studies, differed among the studies. The occurrence of safety events, specifically thromboembolic events, was evaluated at different time points across studies and the occurrence of safety events in relation to reinitiation of anticoagulation was often not documented.

Clinical benefits

Hemostatic efficacy

Hemostatic efficacy is often the focus of clinical trials, but as the panel noted, it may not be the best measure of effectiveness, especially in cases of intracranial hemorrhage (ICH), when functional outcomes may be more important to patients and caregivers. In its guidance, the FDA suggests that a clinical benefit of a reversal agent can be measured by those achieving good or excellent hemostasis.

As noted, there were no head-to-head randomized or observational trials of the reversal agents. Additionally, the majority of trials did not have a comparator arm, limiting the ability to perform “anchored” indirect comparisons or network meta-analysis. Some, but not all trials evaluated effective hemostasis according to standardized definitions (e.g., proposed criteria from the International Society on Thrombosis and Haemostasis [ISTH]¹⁰ or the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors [ANNEXA-4] trial¹¹). Point estimates for hemostatic effectiveness that are derived from studies that share a common definition for effective hemostasis are provided in Table 1.

Based on the ANNEXA-4 or ISTH definition for effective hemostasis, administration of a pharmacological reversal agent is associated with achievement of effective (ISTH criteria) or good to excellent (ANNEXA-4 criteria) hemostasis in 69% to 89% of patients with a factor Xa inhibitor–related major bleed. To date, the ANNEXA-4 trial and the real-world study conducted by Panos and colleagues are the largest cohorts studied.^{11,12} In both studies, the percentage of patients in whom good to excellent hemostasis was achieved is similarly high, with overlapping confidence intervals, despite differences in the patient populations studied and the different mechanisms of action of the reversal agents. It is important to note that point estimates for hemostatic efficacy and effectiveness are specific to the patient populations in which each reversal agent was studied and likely vary depending on the characteristics of enrolled patients, the site of hemorrhage, the methods for assessment of effective hemostasis, and, for the prohemostatic agents, the dose and agent used. As noted in other sections, reversal agents need to be compared in identical patient populations and with a control arm to evaluate whether reversal agents are more effective than supportive care alone and if so, the magnitude of benefit of each.

Mortality

Although mortality is commonly assessed as an outcome, it may not be the most sensitive measure of the clinical benefit of a reversal agent. Since most studies do not have a control arm, it is unclear whether the administration of a reversal agent has a quantifiable impact on the patient’s clinical course or if clinical course and hospital mortality parallel the expected outcomes based on predicted survival at baseline.¹³ Mortality rates for the pharmacological reversal agents, shown in Table 1, vary widely among studies, which is at least partly due to differences in patient populations.

In the ANNEXA-4 trial, the 30-day mortality rate in the spontaneous ICH cohort was 18.8%, which compares favorably with the inpatient mortality rate of 19% in the real-world study of PCC and aPCC conducted by Panos and colleagues.^{11,12} While it is likely that the mortality rate in the latter study would have exceeded 19% if patients had been followed for 30 days, the ANNEXA-4 trial excluded patients who had poor prognoses, while the study by Panos et al included in the mortality rate patients with an admission Glasgow Coma Scale score < 7, those who underwent neurosurgical procedures within 12 hours of admission, those with baseline hematoma volumes > 60 mL, and those not expected to survive 30 days. Similar to the point estimates for effective hemostasis, the point estimates for mortality are specific to the patient populations in which each reversal agent was studied, emphasizing that reversal agents need to be compared in identical patient populations and with a control arm to evaluate whether they have an impact on mortality and if so, the magnitude of that impact.

Table 1. Hemostatic efficacy and mortality

| Reversal agent | Hemostatic efficacy criteria | ICH, no. (%) | Point estimate for hemostatic efficacy | Mortality |
|---|--|-----------------------------------|--|---------------------------------------|
| Andexanet alfa | Good or excellent hemostasis (ANNEXA-4 criteria) ¹¹ | 171/254 (67) | Overall: 82% (95% CI: 77%-87%) | 30-day, entire cohort: 14% |
| | | | ECH: 85% (95% CI: 76%-94%) | |
| | | | ICH: 80% (95% CI: 74%-86%) | 30-day, spontaneous ICH cohort: 18.8% |
| 4F-PCC | Effective hemostasis (ISTH criteria) ¹⁴ | 59/84 (70.2%) | Overall: 69% | 30-day: 27 (32%) |
| | | | ECH: 60% | |
| | | | ICH: 73% | |
| | Good hemostasis (Sarode criteria) ¹⁵ | 36/66 (55%) | Overall: 65% (95% CI: 53%-77%) ICH: 67% | 30-day: 9 (14%) |
| | Good or excellent hemostasis (ANNEXA-4 criteria) ¹⁶ | 32/46 (69%) | Overall: 69% | NR |
| | | | GI: 82% | |
| | ICH: 69% | | | |
| | Good or excellent hemostasis (ANNEXA-4 criteria) ¹⁷ | 37/37 (100%) | Low-dose (mean 24.6 units/kg): 89% | Inpatient: 4 (7%) |
| | High-dose (mean 48.8 units/kg): 89% | | | |
| | Good or excellent hemostasis (ANNEXA-4 criteria) ¹⁸ | 59/59 (100%) | 88% | Inpatient: 10.2% |
| Good or excellent hemostasis (modified ANNEXA-4 criteria) ¹⁹ | Low-dose: 31/57 (54%) | Low-dose (20-34 units/kg): 75.4% | Low-dose: 19.3% | |
| | High-dose: 27/42 (64%) | High-dose (35-50 units/kg): 78.6% | High-dose: 35.7% | |
| Good or excellent hemostasis (ANNEXA-4 criteria) ¹² | 315/315 (100%) | 79.4% (95% CI: 74.6%-83.6%) | Inpatient, PCC + aPCC safety cohort: 126 (19%) | |
| Effective hemostasis (ISTH criteria) ¹⁹ | 21/29 (72%) | Overall: 72.4% | Inpatient: 6 (20.7%) | |
| | | GI: 100% | | |
| | | ICH: 61.1% | | |
| aPCC | Good or excellent hemostasis (ANNEXA-4 criteria) ¹² | 118/118 (100%) | 88.1% (95% CI: 81.4%-93.0%) | PCC + aPCC safety cohort: 126 (19%) |
| | Effective hemostasis (ISTH criteria) ²⁰ | 18/35 (51.4%) | 68.6% | NR |

Abbreviations: 4F-PCC = four-factor prothrombin complex concentrate; ANNEXA-4 = Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors study; aPCC = activated prothrombin complex concentrate; ECH = extracranial hemorrhage; GI = gastrointestinal; ICH = intracranial hemorrhage; ISTH = International Society on Thrombosis and Haemostasis; NR = not reported.

Harms

Thromboembolic events

Andexanet alfa, aPCC, and 4F-PCC carry a boxed warning about the risk of arterial and venous thromboembolic (TE) events.^{1,21,22} The comparative incidence of TE events has not been evaluated and conclusions from current studies are limited because of small sample sizes, lack of a standardized time frame for assessment of TE events, lack of a control group to quantify the background incidence of TE, or inadequate documentation of reinitiation of the anticoagulant. Without head-to-head comparisons, it cannot be determined whether observed differences in TE event rates across studies are due to the intrinsic properties of the reversal agent alone or to an interplay between those properties with the population's baseline characteristics or the timing of anticoagulant reinitiation.

In healthy volunteers, andexanet alfa was associated with transient elevations in D-dimer and prothrombin fragment 1 + 2 levels, which have been attributed to an interaction between andexanet alfa and tissue factor pathway inhibitor.²³ In the ANNEXA-4 safety population, 34 patients (10%) experienced a TE event within 30 days of administration of andexanet alfa. The timing of the TE event in relation to reinitiation of anticoagulation therapy was not reported.¹¹

Prohemostatic agents contain coagulation factors that may promote TE development. Based on the half-life of coagulation factors contained in the prohemostatic agents, a patient could be at risk for a TE event for up to 14 days after administration. Point estimates for the TE event rate in case series using 4F-PCC or aPCC as reversal agents for factor Xa inhibitor–associated major bleeds vary. In the largest observational cohort of PCCs performed to date, 17 of 514 patients (3.3%) treated with 4F-PCC experienced 18 TE events and 8 of 149 patients (5.4%) treated with aPCC experienced 9 TE events during hospitalization.¹² In a pooled analysis of 7 studies (240 patients), the crude TE event rate with use of 4F-PCC for reversal of factor Xa inhibitor–associated major bleed was 4% (95% CI, 1%-8%). When only the 5 studies with short-term (< 30 days) follow-up were included in the analysis, the crude TE event rate was 3% (95% CI, 0%-6%).²⁴

Based on the available studies, it is uncertain whether any of the reversal agents are associated with more thrombotic complications than others, since differences in TE rates may be attributable to factors other than the reversal agent. One factor is recognizing when to restart anticoagulation therapy — at either prophylactic or treatment doses — which should be considered as soon as it is deemed safe.

Other harms

Because andexanet alfa is a modified recombinant protein, it has the potential to trigger antibody development; therefore its immunogenicity must be monitored. In a group of healthy volunteers, 17% developed low titers of non-neutralizing antibodies against andexanet alfa.^{11,23} To date, no antibodies have been detected against factor Xa or factor X in andexanet alfa recipients. Prohemostatic agents may be associated with hypersensitivity and allergic reactions, including severe anaphylactic reactions, that require immediate discontinuation.^{21,22}

Controversies and uncertainties

Several uncertainties remain with regard to the benefits and harms of andexanet alfa. First, the current evidence base cannot either support or refute the hypothesis that reversal agents modify the clinical course of a patient with factor Xa inhibitor–related bleeding because no studies have included a control arm. Additionally, it is unclear which subgroup(s) of patients, if any, are likely to derive the most benefit from use of a reversal agent versus supportive care management. Questions also remain about the effectiveness of reducing anti–factor Xa activity in hemorrhage because the ANNEXA-4 trial failed to demonstrate a significant relationship between hemostatic efficacy and a reduction in anti–factor Xa activity. The optimal

prohemostatic agent is unknown, as are the optimal doses for the prohemostatic agents. Finally, the current evidence base precludes reliable analysis of the comparative effectiveness of the reversal agents and the agents' long-term value cannot be determined without such an analysis.

2.4 Summary

Comparative effectiveness ratings are summarized in Table 2.

Table 2. Comparative effectiveness ratings for pharmacological reversal agents for factor Xa inhibitor–related hemorrhage

| Agent | Evidence rating |
|----------------|--|
| Andexanet alfa | P/I |
| 4F-PCC | Consensus not achieved P/I: 50%; I: 20% |
| aPCC | Consensus not achieved P/I: 40%; I: 30% |
| Between drugs | I |

Abbreviations: 4F-PCC; four-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; I = insufficient/inconclusive; P/I = promising but inconclusive.

Andexanet alfa

Data to support the safety and effectiveness of andexanet alfa is largely limited to the single-arm ANNEXA-4 trial, which demonstrated good to excellent hemostatic efficacy in 82% of patients, a 30-day mortality rate of 14%, and a TE rate of 10%.¹¹ Since there are no studies with a control arm and little data from real-world cohorts to support or refute the findings of the ANNEXA-4 study, the Vizient panel judged the current body of evidence on andexanet alfa to be “promising, but inconclusive,” compared with standard of care (i.e., supportive care and discontinuation of anticoagulant). This rating suggests that based on current evidence, andexanet alfa may provide either a small or substantial net benefit compared with supportive care, but there is a small likelihood that that the comparative net health benefit might be negative.

Prohemostatic agents

Data to support the hemostatic effectiveness of 4F-PCC and aPCC is based on results from multiple retrospective, single-arm case series, many with small sample sizes and heterogeneous populations. A standardized definition to assess hemostatic effectiveness was used in some but not all, and in many studies, methods for assessing effective hemostasis either were not defined or relied on retrospectively collected data. Despite these limitations, the point estimates for hemostatic effectiveness and TE events often overlap among studies.

The panel did not come to a consensus on clinical effectiveness ratings for 4F-PCC or aPCC. A majority of the panel judged the current body of evidence to be “promising, but inconclusive” or “insufficient/inconclusive,” compared with supportive care. The latter rating acknowledges that the limitations in the body of evidence are so serious that no firm point estimate can be given and it is possible that the comparative net benefit of the prohemostatic agents compared with supportive care may range across all 4 categories, from negative to substantial. This rating is common when a drug is used for an off-label indication.

It is interesting to note that 30% of the panel judged the current body of evidence on 4F-PCC and aPCC to be C+ (comparable to or better than supportive care). This rating suggests that based on current evidence, prohemostatic agents may provide a comparable, small, or substantial net health benefit, but are not likely to

be associated with a negative net benefit. No panel member judged the point estimate of andexanet alfa to be C+, suggesting that either the number of studies or experience with prohemostatic agents in practice (rather than literature evidence) may have influenced the comparative effectiveness rating for those agents.

Comparisons between pharmacological agents for reversal of factor Xa inhibitors

The current evidence base prevents reliable comparative effectiveness analyses of the reversal agents. There are no head-to-head trials and in the absence of trials that share a common comparator arm, “anchored” indirect comparisons should not be performed.²⁵ The effect sizes of andexanet alfa and prohemostatic agents for reversal are often indirectly compared using data from studies that share a common definition for effective hemostasis. Results of indirect comparisons may make it appear that andexanet alfa has a larger effect size than prohemostatic agents, but this is misleading because of key differences between studies — study population, baseline severity of illness (particularly for ICH patients), time to administration of reversal agent, and method of follow-up assessment. High-quality comparative effectiveness data will not be available until a currently ongoing head-to-head comparison between andexanet alfa and standard of care (NCT03661528) is completed which is currently expected in the first quarter of 2023. Therefore, the expert panel judged that there is low certainty about the comparative clinical effectiveness of the agents — i.e., an insufficient/inconclusive rating.

3. Expert opinion

3.1. Overview

As outlined in the materials and methods section, panelists were asked to provide their expert opinions on a series of questions related to the clinical application of reversal agents, operational considerations, and cost and value of reversal agents. An agreement of 60% of panel members was considered a consensus.

3.2. Indications for pharmacological reversal

Consensus statement: In addition to local supportive measures, a pharmacological intervention is indicated for reversal of a factor Xa inhibitor–related major bleed (standardized definition, e.g., ISTH definition of a major bleed) when there is clinical suspicion, based on history and/or laboratory evidence, that clinically relevant levels of a factor Xa inhibitor may be contributing to the bleed.

The expert panel felt that the inclusion and exclusion criteria for the ANNEXA-4 study serve as a good outline for determining appropriateness of pharmacological intervention, when supportive care alone is insufficient, for patients experiencing factor Xa inhibitor–related major bleeding. Major bleeding criteria should consider current evidence-based best practices and guidelines and should be applied within the context of each individual patient’s characteristics. For example, definitions of a drop in hemoglobin should be considered in the context of the patient’s baseline hemoglobin and the location of the bleed. Timing of the last dose of factor Xa inhibitor in relation to the major bleed should be evaluated in the context of organ function (e.g., presence of renal or hepatic dysfunction) and available laboratory data. In the absence of medication-specific anti–factor Xa activity assays, available laboratory assays, including but not limited to anti–factor Xa activity assays (e.g., unfractionated heparin), prothrombin time and international normalized ratio may be helpful in determining the presence or absence of clinically relevant anti–factor Xa activity.

Local policies should address the definition of medical futility and when administration of a pharmacological agent is appropriate. Neurology or neurosurgical consultation may be preferred over a Glasgow Coma Scale score alone in determining patient viability. Use of a pharmacological agent in patients requiring surgical intervention may be necessary depending on the urgency of the clinical scenario. Pharmacological

intervention should not be used for routine surgery but made available in extenuating circumstances when surgery cannot be delayed.

3.3. Clinical scenarios in which one pharmacological reversal agent may be favored

In the first-round questionnaire, panelists were asked to identify potential clinical scenarios for which a specific pharmacological reversal agent might be preferred. Informed by the discussion during the virtual meeting, the revised questionnaire provided a list of clinical scenarios in which reversal agents might be used; those for which consensus was reached are listed in Table 3. Although it is not noted in Table 3, it is reasonable to assume that during times of supply challenge or drug shortages, agents may need to be interchanged.

Table 3. Clinical scenarios in which a specific pharmacological intervention might be preferred

| Prohemostatic agents | Andexanet alfa |
|---|---|
| <ul style="list-style-type: none"> • When prolonged reversal is required • When urgent intervention or faster administration time is required • For procedures that require immediate heparinization | In cases of: <ul style="list-style-type: none"> • Heparin allergy • Religious objection to blood products |

Prohemostatic agents

In the absence of comparative data, the panel identified 3 clinical scenarios in which prohemostatic agents may be preferred for use: those in which there is a need for (1) prolonged reversal, (2) urgent intervention or faster administration (e.g., for an exsanguinating bleed), or (3) immediate heparinization.

Andexanet alfa has a short half-life — approximately 1 hour — so reversal of anti-factor Xa activity persists for only 1 to 2 hours after the completion of an infusion.¹ In both healthy volunteers and patients with bleeds, a rebound of anti-factor Xa activity occurred approximately 4 hours after the completion of the infusion.^{11,23} In patients with renal insufficiency, the elimination half-life of factor Xa inhibitors is prolonged, resulting in extended duration of clinically relevant levels of the agent. For such patients, it may be more appropriate to administer prohemostatic agents with longer half-lives.

In clinical situations that require urgent reversal due to an exsanguinating bleed or a rapidly expanding hematoma, andexanet alfa may not have a timely hemostatic effect. Although anti-factor Xa activity was reduced by more than 90% within 2 to 5 minutes of completion of a bolus dose of andexanet alfa in healthy volunteers in the ANNEXA-4 trial, the study failed to demonstrate a significant relationship between reduction in anti-factor Xa activity and hemostatic efficacy.^{11,23} Hemostatic efficacy was assessed at a single time point — 12 hours after the end of the infusion — and time to achieve hemostatic efficacy was not reported.¹¹ In the pivotal trial of the specific reversal agent, idarucizumab, the median investigator-reported time to cessation of bleeding was 11.4 hours, demonstrating that hemostasis was not achieved immediately.²⁶ In patients who are actively hemorrhaging (e.g., an exsanguinating bleed), administration of PCCs that replace lost endogenous coagulation factors, thereby promoting thrombin generation, may achieve hemostasis more quickly.

The ANNEXA-4 trial excluded patients who required emergency surgery.¹¹ Since the approval of andexanet alfa, case reports have been published showing that in patients who require emergency surgery after administration of the agent, subtherapeutic intraoperative heparinization may occur because andexanet alfa binds to the heparin-antithrombin complex. Therefore, use of andexanet alfa may be precluded in cases where intraoperative heparinization is important and surgery is emergent. An alternative anticoagulant (e.g.,

a direct thrombin inhibitor) can be used if andexanet alfa has been administered and intraoperative anticoagulation is required. Conversely, if surgery is not emergent, andexanet alfa has a short-half life and intraoperative heparinization will not be affected if an appropriate period of time has elapsed since the infusion was completed.²⁷

Andexanet alfa

In the absence of comparative data, the panel identified 2 clinical scenarios during which andexanet alfa may be preferred for use: in patients with known heparin-induced thrombocytopenia (HIT) and in those who decline transfusion of specific blood components because of religion.

Four-factor PCC contains a small amount of heparin (8-40 units and 16-80 units of heparin in 500 units and 1,000 units of 4F-PCC, respectively), and its use is contraindicated in patients with known HIT.²¹ Of note, aPCC does not contain heparin and can be used in patients with HIT.²¹ The panel noted that the decision to use 4F-PCC in a patient with a history of HIT will depend on the time lapsed since the occurrence of HIT.

While nearly all Jehovah's Witnesses refuse transfusions of whole blood and the primary blood components (red cells, platelets, white cells), some individuals may accept the transfusion of derivatives of primary blood components, such as clotting factor concentrates. As a result, this clinical scenario may not apply to all Jehovah's Witnesses.

3.4. Combination therapy

Consensus statement: There is no reliable evidence to establish that it is a safe practice to use andexanet alfa and PCC or aPCC in combination. While it is not routine practice, there may be an exceptional clinical situation in which a practitioner may opt to administer both agents or use a second dose of the selected agent.

In the opinion of the expert panel, there is no clinical evidence to support the administration of additional pharmacological interventions, with the same or a different agent, in patients who continue to experience major bleeding. Careful consideration of the risk of thrombosis and benefit of additional therapy is advised and should be tailored to each patient's specific needs. In exceptional clinical scenarios or extenuating circumstances, it may be reasonable to administer a subsequent dose of the same or a different pharmacological agent in patients with major bleeding that has not resolved (i.e., titrate to effect). There is no clinical scenario in which concurrent administration of andexanet alfa and PCC or aPCC is advised. In patients who receive multiple doses of a pharmacological agent, venous thromboembolic prophylaxis should be initiated as soon as clinically safe and reasonable.

3.5. Operational considerations

In the opinion of the expert panel, there are several operational considerations that should be accounted for when determining the role in therapy of PCC, aPCC, and andexanet alfa. All advantages and disadvantages that achieved expert consensus are listed in Table 4. Several considerations, including variation in factor IX concentration between lots of PCC and aPCC and availability of anti-factor Xa assays, did not achieve consensus or were not considered to be either an advantage or disadvantage. Although variation in factor IX concentration among lots may not represent a clinical concern, the panel acknowledged that members may need to establish an operational process locally to dispense and administer PCC or aPCC in a timely manner.

Storage, preparation, and administration were important points of discussion. Andexanet alfa should be stored refrigerated at 2 °C to 8 °C (36 °F-46 °F),¹ whereas PCC and aPCC may be stored at room temperature, not to exceed 25 °C (77 °F).^{21,22} Dissolution time of andexanet alfa is approximately 3 to 5

minutes per vial; five 200-mg vials are needed for low dose and 9 for high dose.¹ Vials should be reconstituted in succession to expedite dissolution. Dissolution of PCC and aPCC occurs rapidly. Both PCC and aPCC may be administered as a slow intravenous (IV) push, whereas andexanet alfa must be further diluted after reconstitution, generally in the pharmacy IV room, for IV bolus and infusion.^{1,21,22} These differences mean that PCC and aPCC can more easily be stored at the point of care and more rapidly accessed and administered. Additionally, members need to establish protocols governing whether andexanet alfa will be supplied as a single preparation or if the bolus and continuous infusion will be prepared separately.

The Joint Commission National Patient Safety Goal for anticoagulant therapy requires organizations to use approved protocols and evidence-based practice guidelines for reversal of anticoagulation and management of bleeding events for each anticoagulant medication.²⁸ While there is no FDA-approved PCC or aPCC dose for factor Xa inhibitor reversal, dosing should be standardized based on the available literature. The ideal doses of PCC and aPCC are unknown, as many dosing strategies have been explored; this may be a limitation of therapy. Conversely, andexanet alfa dosing is FDA approved but may be cumbersome due to the patient information (e.g., which oral factor Xa inhibitor was used, timing of last dose) required for appropriate dose selection.

Lastly, the half-life of each reversal agent may play an operational role. Administration as a continuous infusion is required for andexanet alfa because of its short half-life. This may prevent or delay administration of other agents, since an IV line must be dedicated to andexanet alfa for the course of therapy, but also allows for the infusion to be quickly discontinued if needed. Administration of PCC and aPCC is rapid with sustained effect, allowing administration of other agents in an urgent or emergent clinical scenario.

Table 4. Advantages and disadvantages of reversal agents

| Agent | Advantages | Disadvantages |
|-----------------|--|---|
| 4F-PCC/ aPCC | <ul style="list-style-type: none"> Easier access (point-of-care storage) Shorter reparation and administration time (IV access) Potential for fixed or standard dosing per institutional protocol | <ul style="list-style-type: none"> No FDA-approved dosing (25 units/kg, 50 units/kg) |
| Andexanet alfa | <ul style="list-style-type: none"> Short half-life allows for “turning off” infusion FDA-approved dosing | <ul style="list-style-type: none"> Longer preparation time (larger vial burden, longer dissolution time) Slower administration speed Should not be reconstituted at the bedside because it does not meet the criteria for immediate-use compounding In some circumstances, reconstituted product may not be returned for credit |

Abbreviations: 4F-PCC; four-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; FDA = Food and Drug Administration; IV = intravenous.

3.6. Off-label use

Consensus statement: Use of PCC for reversal of a factor Xa inhibitor–related bleed is ethically and legally justified because guidelines support its use as a standard of care, the FDA permits approved drugs to be used off-label, and there are no prospective comparisons that demonstrate the superiority of andexanet alfa over PCC or aPCC.

The FDA makes it clear that since the agency does not regulate the practice of medicine, the federal Food, Drug, and Cosmetic Act of 1938 will not play a role in creating physician liability for off-label drug use.²⁹ According to the FDA, the tenets for off-label use of a drug are: (1) prescribers have the responsibility to be well informed about the product; (2) use should be based on firm scientific rationale and sound medical evidence; and (3) records of the drug's use and effects should be maintained.³⁰ Because the first factor Xa inhibitor was approved in 2011 — 7 years before the approval of a specific antidote — prohemostatic agents have become entrenched in the standard of care in clinical practice, with varying levels of recommendation by professional organizations. In the opinion of the expert panel, FDA approval status alone does not justify the preferred use of an agent with limited data and no comparative data.

Several guidelines prioritize the use of andexanet alfa as a first-line reversal agent, citing — among other reasons — the FDA approval for reversal and the lack of approvals of prohemostatic agents for this indication. While andexanet alfa was approved in May 2018, its indication as a reversal agent was approved under an accelerated process based on a surrogate outcome — change from baseline in anti-factor Xa activity in healthy volunteers — and its continued approval is contingent on results of studies that demonstrate an improvement in hemostasis in patients.¹ Though the ANNEXA-4 trial evaluated a clinical benefit, defined by the FDA as excellent or good hemostatic efficacy, the study was unable to establish causality because a comparator arm was not included. As a component of its accelerated approval, the hemostatic effect of andexanet alfa must be further described and verified in the ongoing phase 4 postmarketing study.³¹ Past investigations of drugs or indications that were granted accelerated approval show the following trends: (1) postmarketing safety events are more common in drugs that receive expedited approval,³² and (2) confirmatory trials of clinical benefit are substantially delayed³³; of those performed, no more than half confirm clinical benefit.³⁴ The need for confirmatory evidence for continued approval of andexanet alfa and the performance of expedited drugs in confirmatory trials makes its FDA approval a less compelling argument for prioritization as a first-line reversal agent. Without a head-to-head comparison, FDA approval alone does not justify use of an agent with limited data.

4. Value

4.1. Cost as a consideration

Consensus statement: Low utilization of andexanet alfa is not driven by high cost alone. Considerations other than cost — operational and clinical — may also limit its utilization.

Value is defined as the net benefit per cost of a treatment (or service) to an individual patient and is an interplay between the short-term affordability and long-term value of a treatment. Based on short-term budget impact, andexanet alfa is several times more expensive than prohemostatic agents. The October 2020 wholesale acquisition cost (WAC) for a package of four 200-mg vials of andexanet alfa is \$22,000. Based on the current WAC, a low-dose regimen of andexanet alfa costs \$27,500 and a high-dose regimen \$49,500. In contrast, the cost of 4F-PCC for an 80-kg patient who receives 25 to 50 units/kg is \$5,240 to \$10,480, using a WAC price of \$2.62 per unit.

Without comparative effectiveness data to determine whether functional, mortality, or safety differences exist between pharmacological reversal strategies, an assessment of the long-term value of andexanet alfa and prohemostatic agents is reduced to a discussion of benefits and disadvantages of each (see section 2), as well as the contextual considerations. Even at cost parity, the panel noted that a prohemostatic agent may still offer greater value in certain clinical contexts due to its operational advantages — for example, in the case of an exsanguinating bleed. Until more robust comparative data are published, the comparative long-term value is unknown.

Although some have suggested that andexanet alfa is more cost-effective than 4F-PCC based on demonstration of a 30-day mortality benefit, this benefit is based on a matched analysis³⁵ of cohorts from the ORANGE³⁶ and ANNEXA-4 trials. However, the analysis did not match patients based on the severity of brain injury, which is an important confounder because those at high risk of mortality or with severe brain injury were excluded from the ANNEXA-4 but not from the ORANGE trial. It is plausible that the baseline risk of mortality differed between cohorts and the 30-day mortality rate for each cohort is a result of the mortality risk at baseline. The potential differences in mortality between real-world and clinical trial settings can be illustrated by examining the mortality of andexanet alfa in each of these settings. In the ANNEXA-4 trial, a controlled setting with inclusion and exclusion criteria, the mortality rate was 14%, while in the real-world setting, one health system reported a mortality rate of 40% during its initial experience with andexanet alfa.³⁷

4.2 New technology add-on payment

The Centers for Medicare & Medicaid Services provide additional payments, referred to as new technology add-on payments (NTAP), for new, high-cost technologies in the inpatient setting. An NTAP provides an additional amount to hospitals above the standard Medicare severity diagnosis-related group (MS-DRG) payment amount, usually for 3 years from the date of designation. Andexanet alfa received an NTAP designation on October 1, 2018.

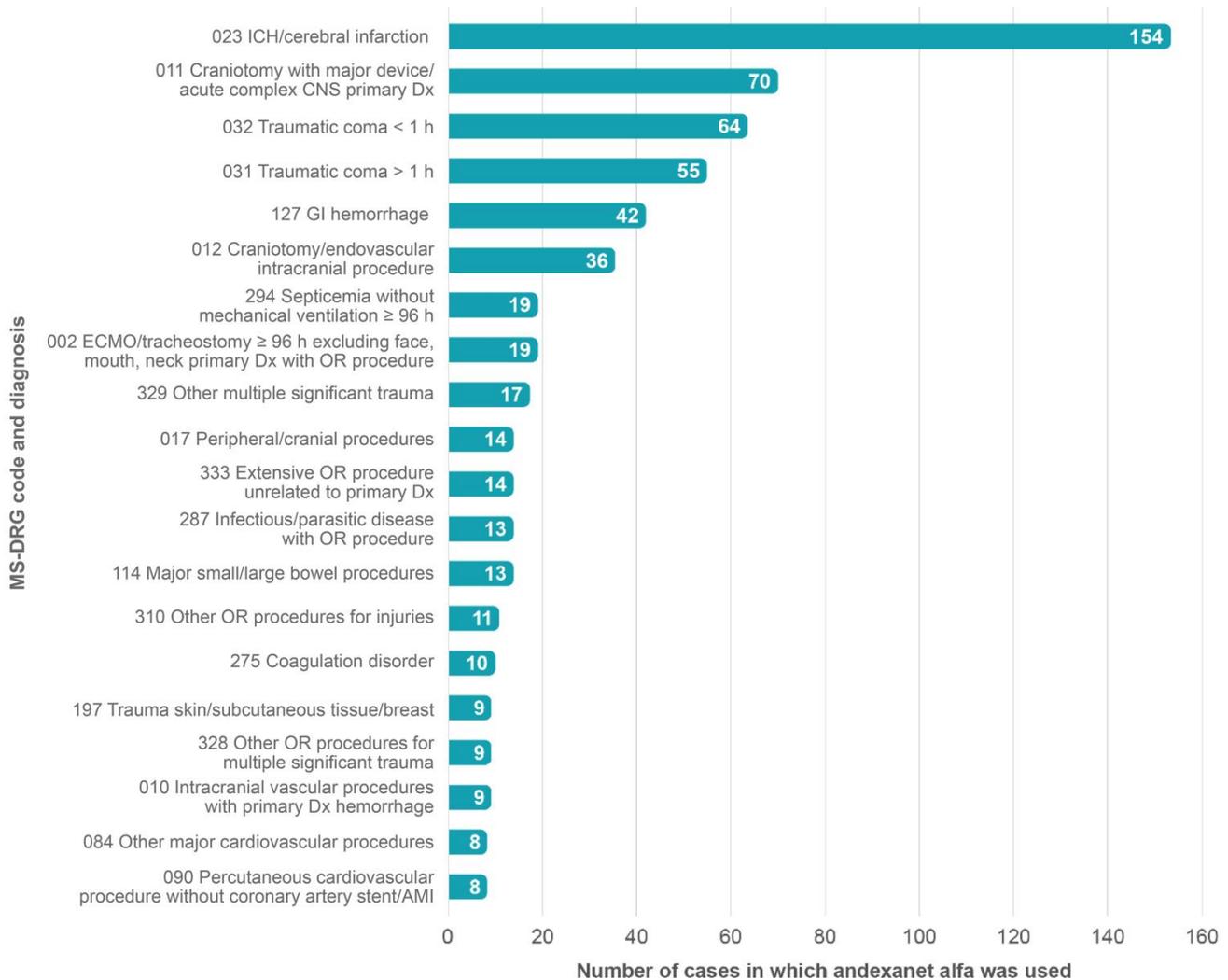
For qualifying Medicare inpatient cases with dates of service on or up to 1 year after October 1, 2019, health systems are eligible to receive, in addition to the MS-DRG payment, an NTAP for andexanet alfa equal to the lesser of 65% of the cost of andexanet alfa or 65% of the amount by which the costs of the case exceed the standard MS-DRG payment, up to a maximum of \$18,281.25. For all services dated prior to October 1, 2019, the NTAP is 50%.³⁸

The NTAP can be collected by health systems for up to 1 year after the date of service. While these additional payments can potentially mitigate the short-term budget impact of andexanet alfa, health systems' billing departments must know how to capture them. It is unknown whether MS-DRG payment amounts will be increased to capture the additional expense of andexanet alfa after the NTAP designation expires.

5. Real-world utilization

Data on the utilization of pharmacologic reversal agents for treatment of iatrogenic bleeding was extracted from the Vizient Clinical Data Base (CDB), an administrative database that includes data from various types of hospitals, from comprehensive academic medical centers to small community hospitals. A review of data from 341 hospitals for calendar year 2019 revealed that 106 hospitals had used andexanet alfa in at least 1 case (median, 3 cases; interquartile range [IQR], 2-10), whereas 340 had used 4F-PCC or aPCC in at least 1 case. Of the 779 cases in which andexanet alfa was administered, 55% were central nervous system processes, as defined by base MS-DRG code. Figure 1 shows the 20 diagnoses, by MS-DRG code, for which andexanet alfa was most often used.

Figure 1. Top 20 diagnoses for which andexanet alfa was used at 106 hospitals in 2019



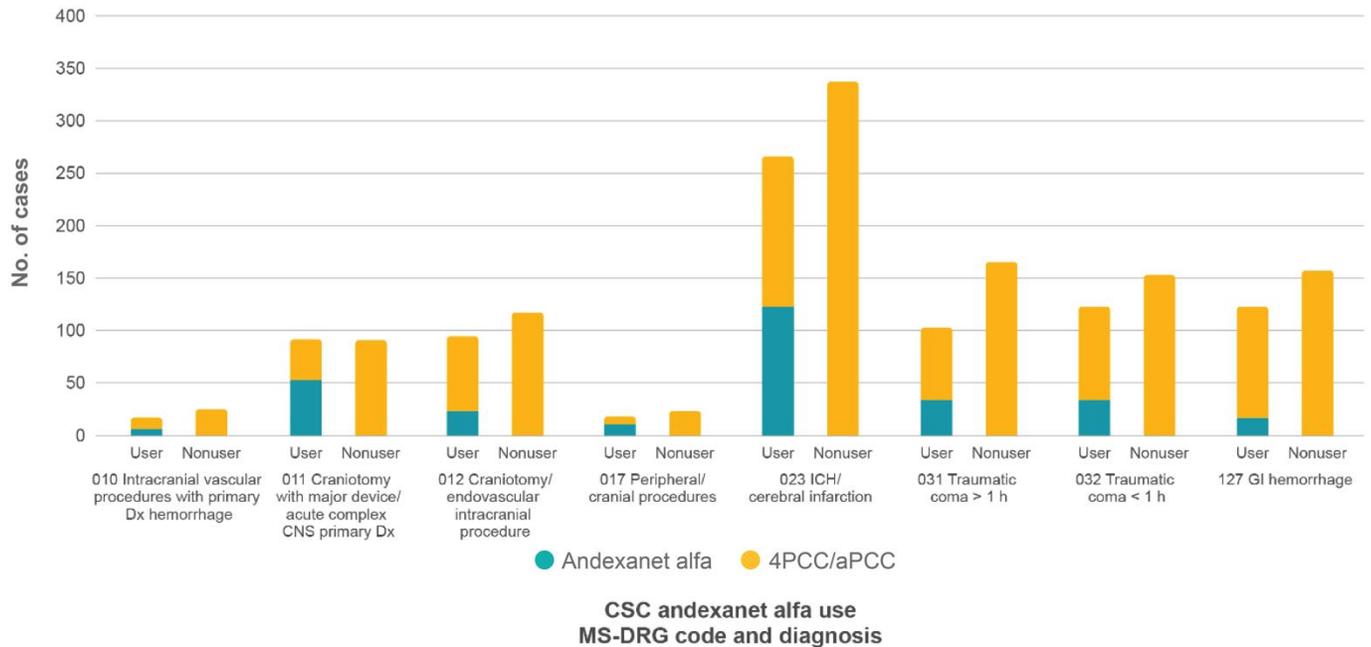
Source: Vizient Clinical Data Base.

Abbreviations: CNS = central nervous system; Dx = diagnosis; ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; ICH = intracranial hemorrhage; MS-DRG = Medicare severity diagnosis-related group; OR = operating room.

Use of 4F-PCC and aPCC was more common and more generalized, with over 10,000 cases in the CDB (excluding cases with concomitant phytonadione use). The most common use was in cardiac valve/other major cardiothoracic procedures without catheterization, followed by ICH (824 cases) and gastrointestinal hemorrhage (619 cases). Although we attempted to eliminate warfarin-related major bleeding cases by excluding cases in which phytonadione was used, it is worth noting that these patients may receive 4F-PCC or aPCC without phytonadione.

Based on the use of reversal agents for ICH, we reviewed use of reversal agents by programs certified by The Joint Commission as comprehensive stroke centers (CSCs). Of the 101 CSCs in the CDB, 57% did not use andexanet alfa during 2019. For the 44 programs that used andexanet alfa in at least 1 case, the median number of such cases per hospital was 11 (IQR, 3-16). Among those programs that had documented use of andexanet alfa and prohemostatic agents, 4F-PCC or aPCC was more often used for intracranial processes than andexanet alfa. Figure 2 shows per-case use of andexanet alfa and 4F-PCC for intracranial bleeding processes and gastrointestinal hemorrhage, categorized by whether the CSC did or did not use andexanet alfa.

Figure 2. Use of reversal agents for 101 CSCs that did and did not use andexanet alfa in 2019



Source: Vizient Clinical Data Base.

Abbreviations: CNS = central nervous system; CSC = comprehensive stroke center; Dx = diagnosis; GI = gastrointestinal; ICH = intracranial hemorrhage; MS-DRG = Medicare severity diagnosis-related group.

We attempted to assess the relationship, if any, between use of a specific pharmacological reversal agent and mortality. The analysis was limited to cases with MS-DRG code 064 (intracranial hemorrhage or cerebral infarction with major complications or comorbidities) and with a diagnosis associated with anticoagulant-associated bleeding (ICD-10 codes z7901, t45515a, d6832, d689) without receipt of phytonadione (Table 5). Overall, the use of any pharmacological reversal agent (andexanet, 4F-PCC, aPCC, combination) in this cohort was low, ranging from 0.2% to 9% of cases. In CSC programs that used andexanet alfa during 2019, the percentage of cases in which andexanet alfa or 4F-PCC/aPCC were administered was the same, at 6% of total cases; however, the incidences of expected and observed death for cases in which 4F-PCC/aPCC were used were higher than for andexanet alfa. Expected and observed mortality were similarly high for cases with use of 4F-PCC/aPCC in which a reversal agent was administered in CSC programs that did not use andexanet alfa for reversal. Overall, the observed-to-expected mortality did not differ significantly among the pharmacological reversal groups, suggesting that choice of agent may be influenced by baseline bleed severity or likelihood of survival.

Table 5. Use of specific pharmacological reversal agents and observed-to-expected mortality in MS-DRG 064 cases (intracranial hemorrhage or cerebral infarction with MCC)

| Hospital uses andexanet alfa? | Total no. of cases | Reversal agent(s) used | No. of cases (%) | Observed deaths, % | Expected deaths, % | Mortality index ^a |
|-------------------------------|--------------------|---------------------------|------------------|--------------------|--------------------|------------------------------|
| Yes | 1,427 | Andexanet alfa | 82 (6) | 20.7 | 27.6 | 0.75 |
| | | 4F-PCC/aPCC | 80 (6) | 35.0 | 30.9 | 1.13 |
| | | Andexanet alfa and 4F-PCC | 3 (0) | 66.7 | 35.9 | 1.86 |
| | | Neither andexanet nor PCC | 1,269 (89) | 19.9 | 19.9 | 1.00 |
| No | 2,648 | 4F-PCC/aPCC | 228 (9) | 36.0 | 36.8 | 0.98 |
| | | Neither andexanet nor PCC | 2,420 (91) | 20.6 | 19.5 | 1.05 |

^a Differences in mortality index between groups were not statistically significant.

Abbreviations: 4F-PCC; four-factor prothrombin complex concentrate; aPCC = activated prothrombin complex concentrate; MCC = major complications or comorbidities; MS-DRG = Medicare severity diagnosis-related group.

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